Staging schema for early diagnosis of prediabetes

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In this Comment, we propose a staging schema for the early diagnosis of prediabetes (intermediate hyperglycaemia) and type 2 diabetes by use of 1-h plasma glucose (1hPG), which was endorsed in a Position Statement by the International Diabetes Federation as a means of identifying people with hyperglycaemia earlier during disease progression to improve long-term outcomes.[1] Screening for prediabetes with 1hPG has been found to be feasible and cost-effective.[1] As there is substantial evidence that people with a high 1hPG (≥155 mg/dL [8·6 mmol/L]) and normal glucose tolerance (NGT) are at increased risk of progression to type 2 diabetes, cardiovascular complications, and premature mortality, lifestyle intervention should be prescribed.[1] Furthermore, it is recommended that the 1-h 75 g oral glucose tolerance test (OGTT) should be added to current screening laboratory measurements, including fasting plasma glucose (FPG), 2-h plasma glucose (2hPG), and HbA_{1c}. A 1hPG of 209 mg/dL or greater (≥11·6 mmol/L) constitutes type 2 diabetes, which warrants a repeat test to confirm the diagnosis.[1]

Cross-sectional studies have shown that, compared with people with NGT and a low 1hPG (<155 mg/dL [8·6 mmol/L]), people with NGT and a high 1hPG manifest both core defects characteristic of type 2 diabetes—β-cell dysfunction and insulin resistance. Insulin clamp studies have shown a 23% reduction in total body insulin-mediated glucose disposal in people with NGT and a high 1hPG, which was similar to the 26% reduction in people with impaired glucose tolerance (IGT). A 30% reduction in first-phase insulin secretion (the strongest predictor of future type 2 diabetes) was reported in people with NGT and a high 1hPG compared with people with NGT and a low 1hPG.[2] Reduction in first-phase insulin secretion and worsening hepatic insulin resistance result in impaired suppression of hepatic glucose production following a glucose load, explaining the excessive rise in plasma glucose concentration at 1 h during the OGTT.[3]

A longitudinal study in a high-risk population found that the insulinogenic index was higher in people with NGT and a low 1hPG than in people with NGT and a high 1hPG (5·3 [SD 4·6] *vs* 3·4 [2·3]); the insulinogenic index was not further reduced in people with IGT (4·2 [7·8]), but declined in people with type 2 diabetes (1·5 [1·2]).[4] The Matsuda insulin sensitivity index (ISI) and the oral disposition index (oDI) progressively decreased from NGT and a low 1hPG (ISI 2·2 [SD 1·0]; oDI 10·6 [SD 12·3]), to NGT and a high 1hPG (1·7 [0·7]; 4·6 [2·0]), to IGT (1·2 [1·6]; 4·4 [6·8]), and to type 2 diabetes (0·8 [0·3]; 1·1 [0·8]).[4] Collectively, these observations suggest that a high 1hPG identifies people at high risk of future type 2 diabetes independent of FPG and 2hPG concentrations. The high 1hPG in people with NGT was found to precede progression to IGT and type 2 diabetes.[4] Confirmation of these results from a larger study in a different population has been carried out and outcomes are awaited. The majority (>90%) of people with IGT have an elevated 1hPG, which might explain the absence of further deterioration in β-cell function when compared with people with NGT and a high 1hPG. The progressive decline in β-cell function across the spectrum of prediabetes was recently confirmed.[5]

The Prediabetes Lifestyle Intervention Study showed that remission from prediabetes to NGT was associated with improvement in insulin sensitivity and reduced visceral adipose tissue.[6] The US Diabetes Prevention Program showed that regression from prediabetes to NGT was associated with greater improvement in insulin secretion and a lower FPG and 2hPG at baseline.[7] Participants who had achieved NGT at least once reduced their risk of incident type 2 diabetes by 56% in the post-trial Diabetes Prevention Program Outcomes Study, compared with those who never achieved NGT.[8] The higher the frequency of NGT, the more likely that remission of prediabetes could be achieved.[8] The benefit of intervention tends to attenuate with time, suggesting that intervention at the stage of IGT might be too late for arresting decline in β-cell function. Thus, during the lengthy trajectory of prediabetes proximal to the onset of type 2 diabetes, remission is more likely if changes in β-cell function are detected earlier than what is feasible based on current diagnostic thresholds.[9] As the high 1hPG in people with NGT is a sensitive indicator of a decrease in first-phase insulin secretion occurring before IGT and type 2 diabetes, intervening at this earlier timepoint could have the greatest benefit for preserving or improving β-cell function, and avoiding the progressive and precipitous decline in β-cell function before the onset of type 2 diabetes.[1,4,5,9]

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	Risk	Pathophysiology[4,5]		Category	Laboratory
		Insulin secretion	Insulin sensitivity		
Stage 0	Low	+++++	+++++	NGT with 1hPG <155 mg/dL (8·6 mmol/L)	FPG <100 mg/dL (5·6 mmol/L), 2hPG <140 mg/dL (7·8 mmol/L), and HbA_{1c} <5·7% (39 mmol/mol)
Stage 1	Moderate	++	+++	1hPG ≥155 mg/dL (8·6 mmol/L) with NGT	FPG <100 mg/dL (5·6 mmol/L), 2hPG <140 mg/dL (7·8 mmol/L), and HbA_{1c} <5·7% (39 mmol/mol)
Stage 2	High	++	++	1hPG ≥155 mg/dL (8·6 mmol/L) with prediabetes	FPG 100–125 mg/dL (5·6–6·9 mmol/L), 2hPG 140–199 mg/dL (7·8–11·1 mmol/L), or HbA_{1c} 5·7–6·4% (39–46 mmol/mol), or a combination
Stage 3	Type 2 diabetes	+	+	Overt type 2 diabetes	FPG ≥126 mg/dL (7·0 mmol/L), 1hPG ≥209 mg/dL (11·6 mmol/L), 2hPG ≥200 mg/dL (11·1 mmol/L), or HbA_{1c} ≥6·5% (48 mmol/mol), or a combination

Symbols +++++ to + define incremental insulin secretion and insulin sensitivity from good to worst. NGT=normal glucose tolerance. 1hPG=1-h plasma glucose. FPG=fasting plasma glucose. 2hPG=2-h plasma glucose.

Table: **Staging schema of glucose tolerance**

The table illustrates the proposed staging schema of glucose tolerance based on the pathophysiological progression from NGT to type 2 diabetes. Individuals at stage 0 are at low risk for type 2 diabetes, although they might have risk factors (eg, excess weight, family history, and sedentary lifestyle) or an abnormal score on validated screening tools (eg, Finnish Diabetes Risk Score or the American Diabetes Association Risk Test), or both. People at this stage would undergo laboratory testing, including traditional testing modalities (FPG, 2hPG, and HbA_{1c}) or the 1-h OGTT.[10] Given the potential for discordance and underestimation of disease severity when using FPG or HbA_{1c} alone or in combination (which might overlook people with an elevated 1hPG or 2hPG, or both), the inclusion of a 1-h or 2-h OGTT is highly recommended to discriminate from people at later stages of disease.[1] If there is no subsequent worsening of risk factors, laboratory assessment can be repeated every 3–5 years.

Stage 1 is the earliest phase in the deterioration of glucose tolerance. People in this category with a high 1hPG are at moderate risk for type 2 diabetes and should be prescribed intensive lifestyle modifications and followed up frequently (eg, 3–6 months) to ensure return to a low 1hPG.

The development of IGT in people with NGT with a high 1hPG represents further deterioration in glucose tolerance and is designated stage 2. People at this stage are at high risk for type 2 diabetes and should receive intensive lifestyle modifications. Although a prospective intervention study in people with a high 1hPG would be important, the size, cost, complexity, and duration of such a study might make this prohibitive in the near future. Although there is little available evidence supporting lifestyle prescription, this strategy still benefits patients' overall health. Pharmacological therapy could be considered if a patient does not show substantial improvement in glycaemic parameters within a short timeframe (eg, 3–6 months).

The development of overt type 2 diabetes represents a further deterioration in glucose tolerance and is designated stage 3. People at this stage should undergo confirmatory laboratory testing and referral for appropriate management based on their glycaemic (pathophysiological) phenotype.

Detecting people with undiagnosed stage 1, which precedes IGT or type 2 diabetes (stages 2 and 3), will alert both the individual and health-care providers of the potentially progressive nature of prediabetes and the need to intervene early to reverse or prevent progression. Endorsement of this schema by scientific organisations should enhance global health and mitigate the diabetes pandemic.

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